

PRIMARY EFFICACY ENDPOINT

The **primary endpoint** of the HEP002 study was to evaluate the ureagenesis improvement at 6-month post first infusion day (FU visit 3). The improvement at 3, 9 and 12 months were also evaluated as secondary efficacy objective. All results pertaining to the ^{13}C test results are presented together hereafter. A total of 3 patients received infusions of HepaStem, of whom one was prematurely discontinued after the first infusion.

Individual profiles showed large inter and intra-variability:

- At baseline, 2 patients (ASLD and CPSID) presented a baseline kinetic with maximum concentration reached 30 minutes after ingestion which might have dragged the median up.
- No post-baseline kinetic was performed for the patient with ASSD who received only one HepaStem infusion and prematurely discontinued the study.
- During the BL period, for the patient with ASLD, the maximum ^{13}C urea concentrations were generally observed 30 minutes after sodium acetate ingestion. At the third BL visit, the maximum ^{13}C urea concentration was largely above the maximum concentration observed at the 2 previous visits. The assessments performed at the FU visits 1 and 5 (3 and 9 months after HepaStem infusion), showed maximum concentration 60 minutes after marker ingestion. The kinetics at FU visits 3 and 7 (6 and 12 months) were very similar to those observed at BL.
- Following HepaStem infusions, the patient with CPSID had peak ^{13}C urea concentrations largely above those observed at BL suggesting an improvement in ureagenesis. Twelve (12) months after HepaStem infusion, maximum concentration was also reached at about 60 minutes after ingestion, with the concentrations at plateau being above the concentrations observed at baseline. However, values at 6 month FU were within the range observed at baseline.

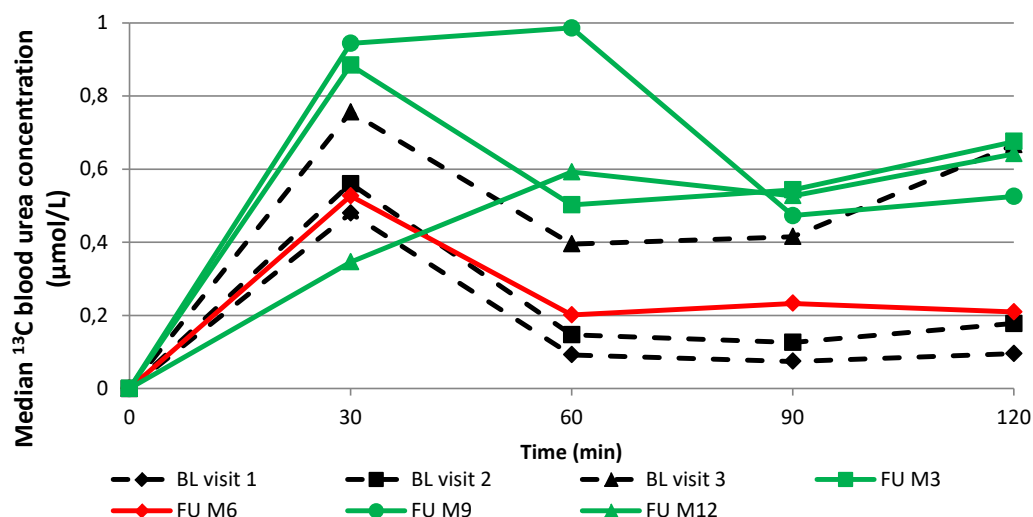
When the data collected during the BL were considered ($N = 3$), median $\text{AUC}_{0-120 \text{ min}}$ was $33.390 \text{ min} \cdot \mu\text{mol/L}$ and exhibited a large variability (range: 13.07; 70.02 $\text{min} \cdot \mu\text{mol/L}$). Following HepaStem infusions ($N=2$), median $\text{AUC}_{0-120 \text{ min}}$ appeared to be slightly above BL values with $67.995 \text{ min} \cdot \mu\text{mol/L}$ (range: 61.71; 74.28) at the 3-month FU visit and $79.973 \text{ min} \cdot \mu\text{mol/L}$ (28.80; 131.15) at the 9-month FU visit compared to baseline (median ranging between 20.775 [at BL visit 1] and 57.030 $\text{min} \cdot \mu\text{mol/L}$ [at BL visit 3]). These results suggested an improvement in ureagenesis during the 3 first months following the infusion of HepaStem for the 2 patients who completed the infusion protocol.

Individual data confirmed the increase in $\text{AUC}_{0-120 \text{ min}}$ at the 3-month follow-up visit compared to baseline:

- Baseline $\text{AUC}_{0-120 \text{ min}}$ also showed large intra-individual variability at baseline for the 2 patients who received the HepaStem infusion as per protocol. A high value was observed at the third BL visit. However, the $\text{AUC}_{0-120 \text{ min}}$ appeared to be increased at the first FU visit (3 months post HepaStem infusion).
- $\text{AUC}_{0-120 \text{ min}}$ for the patient with ASLD got back to values within ranges observed at BL from the 6-month FU visit on.

- The patient with CPSID seemed to maintain high $AUC_{0-120 \text{ min}}$ values up to the 12-month follow-up visit.

Figure: ^{13}C blood urea concentration ($\mu\text{mol/L}$) over baseline and follow-up periods – Safety set (N=3)



BL: baseline; FU: follow-up; M: month

In black, baseline visits; in red, primary objective (6-month FU), in green, secondary objectives

Table: $AUC_{0-120 \text{ min}}$ over the baseline and follow-up periods – Safety set (N=3)

$AUC_{0-120 \text{ min}}$ ($\text{min} \cdot \mu\text{mol/L}$)		
Baseline period		
Visit 1; N=3	Mean (SD)	34.250 (31.290)
	Median [range]	20.775 [11.96 ; 70.02]
Visit 2; N=3	Mean (SD)	42.400 (34.728)
	Median [range]	33.390 [13.07 ; 80.75]
Visit 3; N=3	Mean (SD)	53.725 (13.602)
	Median [range]	57.030 [38.78 ; 65.37]
Follow-up period		
FU 1 (3 months); N=2	Mean (SD)	67.995 (8.888)
	Median [range]	67.995 [61.71 ; 74.28]
FU 3 (6 months); N=2	Mean (SD)	31.935 (30.653)
	Median [range]	31.935 [10.26 ; 53.61]
FU 5 (9 months); N=2	Mean (SD)	79.973 (72.369)
	Median [range]	79.973 [28.80 ; 131.15]
FU 9 (12 months); N=2	Mean (SD)	53.573 (73.408)
	Median [range]	53.573 [1.67 ; 105.48]

$AUC_{0-120 \text{ min}}$: Area under the drug concentration-time curve calculated between 0 and 120 min; FU: follow-up, SD: standard deviation; NA: not applicable